

Endocrine Disrupting Chemicals and Female Fecundity: Implications for Health Across the Lifespan

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October 30, 2019



Today's talk

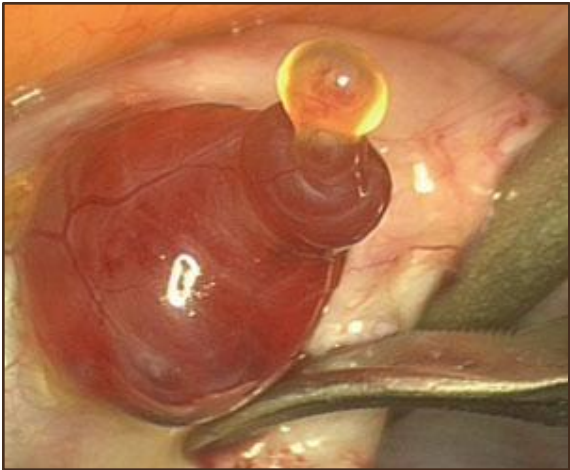
Issue	EDCs	Fecundity	Health - Lifespan
Why important to research?	<p>Prevalent in modern environments</p> <p>Interfere with hormones</p>	<p>Biologic capacity for reproduction</p> <p>Marker disease risk - lifetime & generations</p>	<p>1° and 2° prevention</p>
What we know?	<p>Readily measurable mixtures</p> <p>Lifestyle exposures</p>	<p>Associations for several EDC classes</p> <p>No evidence 'vitamin'</p>	<p>Health is a continuum not just absence of disease</p>
What's needed?	<p>Sensitive windows</p> <p>Mixture analytics</p>	<p>Population biomarker</p> <p>Couple dependent</p>	<p>Causal pathways</p> <p>Interventions</p>

Endocrine Disrupting Chemicals

“...exogenous chemical, or mixture of chemicals, that interfere with any aspect of hormone action.”
(Zoeller et al. 2012)



Sensitive Windows & Hidden Outcomes (at population level)



EDCs & Diminished Fecundability

(as measured by a significantly longer time-to-pregnancy)

EDCs	Authors
PCB; HCB	Buck et al. 2002
PCB #153	Axmon et al. 2005
Mercury	Cole et al. 2006
PFOA: PFOS	Fei et al. 2009
PFOA; PFHxS	Vélez et al. 2015
PBDE #100 & 153	Harley et al. 2010
TCDD	Eskenazi et al. 2010
Phthalates	Buck Louis et al. 2014
Triclosan	Vélez et al. 2015

Couple based cohorts

Persistent EDCs & Couple Fecundability

Chemical Class		Female FOR (95% CI)	Male FOR (95% CI)
Lead			0.83 (0.70, 0.98)
<i>p,p'</i> -DDE			0.83 (0.70, 0.97)
PCBs	101		1.28 (1.09, 1.51)
	118	0.82 (0.68, 0.98)	
	138		0.71 (0.52, 0.98)
	156		0.77 (0.62, 0.96)
	157		0.83 (0.70, 0.97)
	167	0.79 (0.64, 0.97)	0.82 (0.70, 0.96)
	170		0.74 (0.56, 0.98)
	172		0.82 (0.68, 0.99)
	209	0.82 (0.71, 0.95)	0.78 (0.65, 0.94)
PFOSA		0.82 (0.71, 0.95)	

Non-persistent EDCs & Fecundability

Chemical Class	Female FOR (95% CI)	Male FOR (95% CI)
Phthalates		
mMP		0.80 (0.70, 0.93)
mBzP		0.77 (0.65, 0.92)
mBP		0.82 (0.70, 0.97)
BP-UV filters		
BP-2		0.69 (0.49, 0.97)
Parabens		
MP	0.63 (0.41, 0.96)	

Buck Louis et al. 2014-2016; Smarr et al. 2017

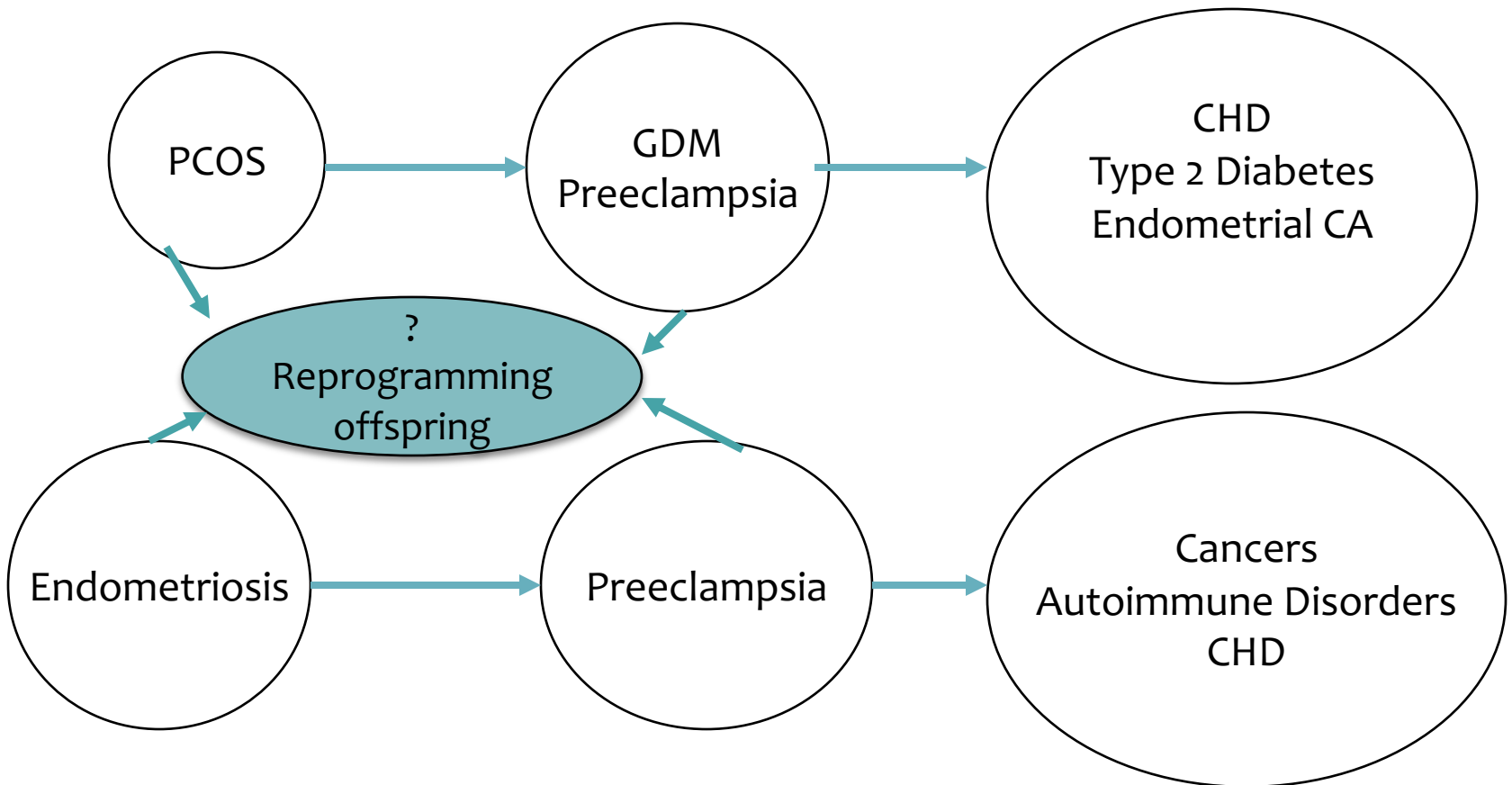
EDCs & female fecundability: Two-Generations

EDC	FR (95% CI) All unprotected intercourse times	FR (95% CI) Restricted to planned times
Serum PCB ($\mu\text{g/L}$):		
<2.5	referent	referent
2.5 – 7.4	0.60 (0.36, 0.99)	0.50 (0.29, 0.89)
>7.4	0.42 (0.20, 0.88)	0.30 (0.13, 0.68)

EDCs & Endometriosis

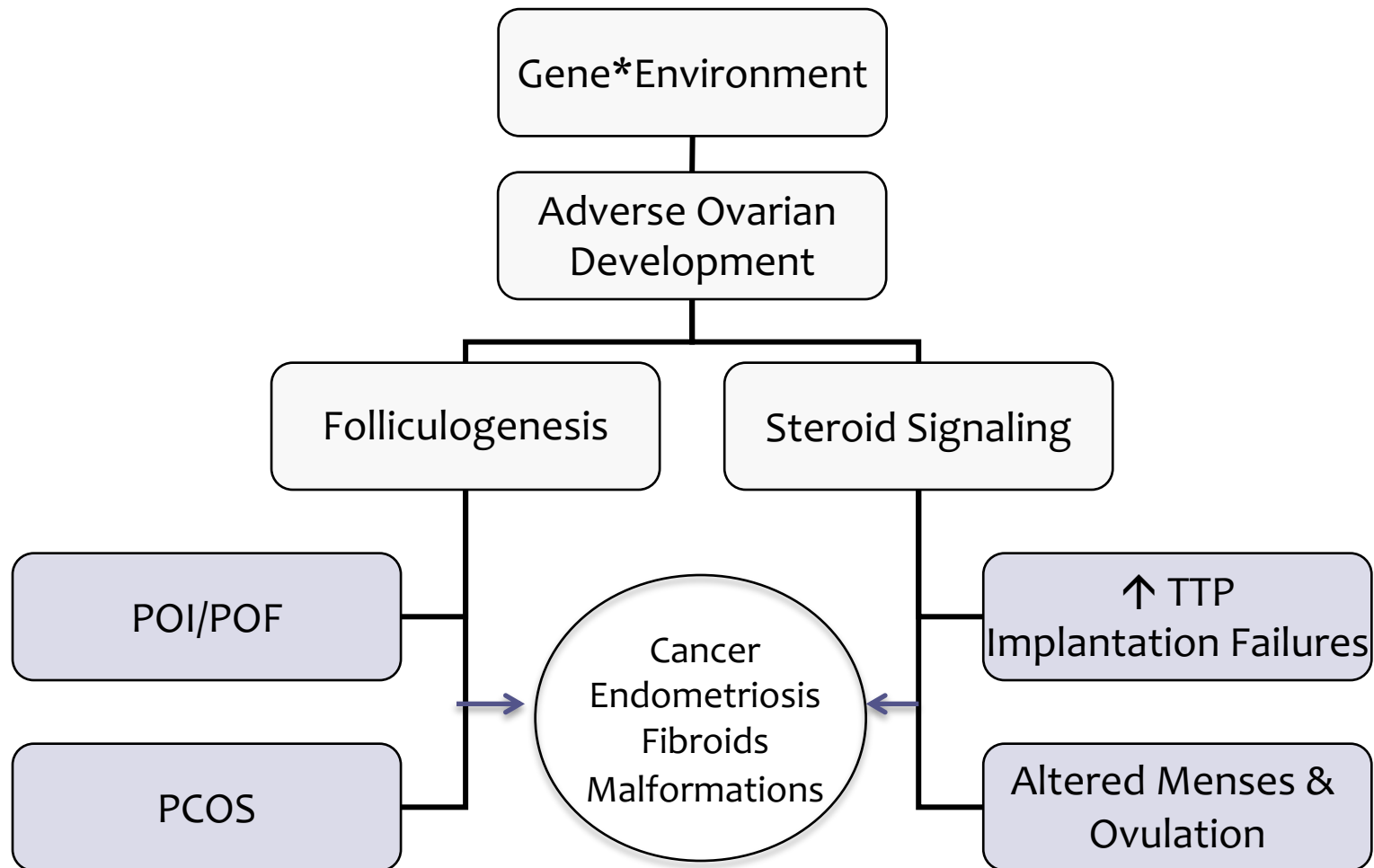
EDC Class	Authors		
PCBs	Buck Louis et al. 2005 Porpora et al. 2006 & 2009		
Phthalates	Reddy et al. 2006 Buck Louis et al. 2013	EDC	OR (95% CI)
Dioxin Σ TEQ	Heilier et al. 2006 Simsa et al. 2010	Dioxin	1.65 (1.14, 2.39)
Cadmium Chromium; copper	Jackson et al. 2008 Pollack et al. 2013	PCBs	1.70 (1.20, 2.39)
HCB γ-HCH; β-HCH β-HCH	Cooney et al. 2010 Buck Louis et al. 2012 Upson et al. 2013	OCPs	1.23 (1.13, 1.36)
PFOA; PFNA	Buck Louis et al. 2012	Cano-Sancho et al. Environ Int 2019	
Benzophenones	Kunisue et al. 2012		

Are fecundity impairments in the pathway to later onset disease?



Reproduction: the 6th vital sign (Cedars et al., 2017)

Ovarian Dysgenesis Syndrome (ODS)



Policy Considerations: EDCs & Women's Health

Population Implications

- Fecundity impairments
- Gravid health disorders
- Later onset adult disease
- Multi/trans-generational effects

Clinical Implications

- Early marker of later disease
- Higher risk of adverse perinatal & neonatal outcomes

If pregnancy is the ultimate stress test...
is reproductive health the (bio)marker of population health?

Policy Considerations: Costs of EDCs

European Union

- PBDEs ‘caused’
 - 4,615 cryptorchidism cases costing €130 million
 - 6,830 testicular cancers costing €848 million
- Phthalates ‘caused’
 - 618,000 ART procedures costing €4.71 billion
 - 145,000 endometriosis diagnoses costing €1.25 billion
- DDE ‘caused’
 - 56,700 fibroid diagnoses costing €163 million

Hauser et al. 2015; Hunt et al. 2016

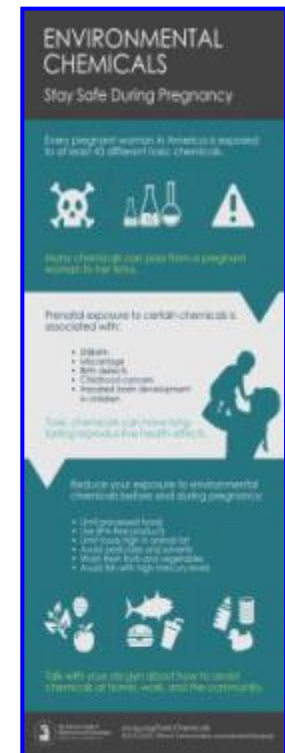
United States

- EDCs
 - Expenditures estimated at \$340 billion (2.33% GDP) using Monte Carlo simulations for 15 exposure-response scenarios with uncertainty factors

Attina et al.2016

Action - Supporting Earlier & Continuing Calls

- Fill data gaps
 - Are fecund (fertile) people healthier?
 - Does gynecologic health inform later onset diseases?
 - Do fecundity impairments impact offspring's health?
- Empirically-based guidance
- Prevention strategies





#CHHS2020
#MakingHealthVisible



**Collaborative on
Health and the
Environment**



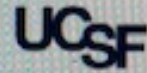
Program on Reproductive Health
and the Environment



FIGO

International Federation of
Gynecology and Obstetrics

the Global Voice for Women's Health



EaRTH Center

Environmental Research and Translation for Health

**ENDOCRINE
SOCIETY**



Alliance of Nurses for
Healthy Environments



IFFS

INTERNATIONAL FEDERATION OF FERTILITY SOCIETIES

Fédération internationale des sociétés de fertilité

Federación internacional de sociedades de fertilidad

EDCs – modes of action

(targeting reproductive tissue and function)

- Epigenome reprogramming through germline
- Disruption of HPG axis
- Perturbations in hormonal system... hormone receptors
- Modified regulation of mRNA & miRNA expression

Reviews: Crain et al. 2008; Fowler et al. 2012; Rattan et al., 2017; Cano-Sancho et al. 2019

Chemical Classes

Commercial Uses

Organochlorine pesticides (OCPs)
(mixed)

Pesticides

Polybrominated biphenyls (PBBs)
(estrogenic)

Plastic additive to prevent burning
(computers, TVs)

Polybrominated diphenylethers (PBDEs)
(mixed)

Flame retardant used in foams, textiles,
plastics

Polybrominated biphenyls (PCBs)
(mixed)

Insulating fluids; paint additives

Polyfluoroalkyl (PFASs)
(estrogenic)

Coatings/products that resist heat, oil,
stains, grease, water; nonstick cookware

Bisphenol A (estrogenic)

Polycarbonate plastics; coatings in canned
foods; medical devices; sealants

Phthalates (anti-androgenic)

Flexible plastics; matrix in cosmetics;
medical devices; enteric coatings

Benzophenone UV-filters (mixed)

Sunscreens; minimize fading

Parabens (estrogens)

Preservatives, anti-microbials;
medications

Reproductive Outcomes & Later Onset Disease*

Reproductive Outcomes	Adult Disease
Fecundity impairments GDM, PCOS	↑ risk T2D, CHD, metabolic syndrome, stroke, endometrial cancer
Endometriosis	↑ autoimmune disorders, cancer risk, CHD
Gravid disorders PCOS, pre-eclampsia, GDM	↑ risk cancer, CHD & metabolic disorders, ↑ risk T2D
Perinatal Girls born early or small	Earlier puberty, ↑ risk GDM & metabolic disorders, earlier menopause

*Observational research